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# FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF BAMBUTEROL HYDROCHLORIDE

**Nayan N. Vadsola* and Bijal Prajapati**

Department of Pharmaceutics, Parul Institute of Pharmacy, Limda, Vadodara, Gujarat (India).

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***Corresponding Author'**
**Nayan N. Vadsola**
Department of Pharmaceutics, Parul Institute of Pharmacy, Limda, Vadodara, Gujarat (India).

## ABSTRACT

The aim of present work was to formulate and evaluate mouth dissolving tablet of Bambuterol Hydrochloride to minimize the disintegration time and improve % drug release. Bambuterol Hydrochloride is an Antiasthmatic drug. Mouth dissolving tablet was formulated using Camphor as a subliming agent. Sodium deoxycholate and Cross povidone were added as permeation enhancer and as a super-disintegrant respectively. Optimization was done by $3^2$ full factorial design and developed formulation was evaluated for *In-vitro* drug release study and Ex-vivo diffusion study. Concentration of Camphor and Sodium deoxycholate were selected as independent variables. All formulations were evaluated for properties such as weight variation, hardness, friability, drug content, disintegration time, wetting time study, *In-vitro* dissolution study, Ex-vivo diffusion study. % *In-vitro* drug release and % Ex-vivo permeation at 10 min were selected as dependent variables. Analysis of variance was performed for dependent variables. *In-vitro* release data was fitted to various kinetic models of drug release. Optimized formulation batch (B9) had complies the acceptance criteria and was found to be stable for 1 month. % In vitro drug release and % ex-vivo permeation of optimized formulation were found to be 90% and 78.46% at 10 min respectively.

**KEYWORDS**: Antiasthmatic drug, Super-disintegrating agent, Sublimation method, Mouth dissolving tablet, $3^2$ full factorial designs.

## 1. INTRODUCTION[1-3]

Asthma related various disorders of the respiratory system leads to difficulty in breathing. It causes the respiratory airways hyper reactive to various stimuli. Asthma is a common chronic

inflammatory disease of the airways characterized by various recurring symptoms like bronchospasm, air way inflammation and airflow obstruction.

Mouth dissolving tablet is describe as "A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly within a few seconds when placed on to tongue." According to European pharmacopoeia, these mouth dissolving tablets (MDTs) should disintegrate in less than three minutes. No need of drinking water.

Bambuterol Hydrochloride (BHT) is the bisdimethylcarbamate prodrug of terbutaline. The adrenergically inactive bambuterol has in itself a high affinity for lung tissue but to become effective, it must be administered systemically, preferably by the oral route. BHT is a direct acting sympathomimetic with predominantly β2-agonist. It is an ester prodrug of β2 adrenergic agonist terbutaline. It is used for the prophylaxis and treatment of chronic asthma and chronic bronchitis in pediatrics.

## 2. MATERIALS AND METHODS[4]

### Materials

Bambuterol Hydrochloride was used as an active pharmaceutical ingredient. Bambuterol Hydrochloride was obtained from Shreeji Pharma. Pvt. Ltd. (Vadodara, Gujarat). Camphor, Sodium deoxycholate, Magnesium stearate, Talc, Crospovidone, Microcrystalline cellulose were obtained from Chemco Chemdyes Corp. (Rajkot, Gujarat).

### Method of preparation: Sublimation method

Weigh all the ingredients and pass through 60# sieve separately. Mix properly for 10 min. Add lubricant and glidant, again mix. Compress the blend into 100 mg tablet by single punch rotary compression machine using of 6mm punch. Tablets were then placed in vacuum oven at 60$^{o}$ C for 30 min. till a constant weight of tablet was obtained.

### Screening study of sublimating agents and permeation enhancers [5]

Four (A1 to A4) batches were prepared for screening of formulation.

**Table 1: Screening batches: A1 to A4.**

| Ingredients (mg) | $A_1$ | $A_2$ | $A_3$ | $A_4$ |
|---|---|---|---|---|
| Bambuterol hydrochloride (API) | 10 | 10 | 10 | 10 |
| Camphor | 5 | 15 | - | - |
| Ammonium bicarbonate | - | - | 5 | 15 |

| | | | | |
|---|---|---|---|---|
| Sodium deoxycholate | 3 | 5 | - | - |
| Sodium lauryl sulfate | - | - | 0.5 | 1 |
| Crosspovidone | 6 | 6 | 6 | 6 |
| Talc | 1 | 1 | 1 | 1 |
| Magnesium stearate | 1 | 1 | 1 | 1 |
| Microcrystalline cellulose | Q.S. | Q.S. | Q.S. | Q.S. |
| **Total weight(mg)** | **100mg** | **100mg** | **100mg** | **100mg** |

**$3^2$ Full Factorial Designs[5]**

The concentration of Camphor and concentration of Sodium deoxycholate were selected as independent variables. The % *in vitro* drug release and % Ex-vivo permeation were selected as dependent variables.

In this design, two factors were evaluated each at 3 levels in such a way that low level was (-1), medium level (0) and high (+1).

The results obtained from the experiment were statistically analyzed for response variables by using Design expert 10.0.0 version.

**Table 2: Composition of $3^2$-full factorial design formulations.**

| Ingredients (mg) | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
|---|---|---|---|---|---|---|---|---|---|
| **API** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Camphor** | 5 | 5 | 5 | 10 | 10 | 10 | 15 | 15 | 15 |
| **Sodium deoxycholate** | 3 | 4 | 5 | 3 | 4 | 5 | 3 | 4 | 5 |
| **Crosspovidone** | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| **Talc** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Magnesium stearate** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Micro-crystalline cellulose** | Q.S. | Q.S. | Q.S. | Q.S. | Q.S. | Q.S. | Q.S. | Q.S. | Q.S. |
| **Total weight (mg)** | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg |

**Preformulation study[6]**

It was carried out including of Identification of drug, Solubility study and Drug-excipients compatibility study**.**

**Evaluation parameters of powder blend[7]**

It was carried out by performed of flow property like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio.

**Evaluation parameters of tablet**[8]

Evaluation of tablet was done by Diameter & Thickness, Weight variation testing, Hardness, Friability (%), Drug content, Disintegration Time, % *In-vitro* drug release study, Ex-vivo diffusion study and Wetting time study.

**Kinetic release** study was applied for % drug release data.

**Stability study**[9] of optimized batch was studied at accelerated condition.

**Statistical study**[10]

Design Expert 10 (32-bit) or Stat-Ease software was used to determine the influence of factors on the responses and for the optimization of formulation. We applied $3^2$ factorial design. Result of the statistical study was interpreted from ANOVA analysis.

Statistical study was expressed in the form of polynomial equation as given below:

$$Y=\beta_o+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_1X_1^2+\beta_2X_2^2$$

## 3. RESULT AND DISCUSSION

### ➢ EVALUATION OF TABLET

**Screening study for sublimating polymers**

**Table 3: Disintegration time of screening formulations.**

| Batch No. | Disintegration time(sec) ± SD (N=3) |
|---|---|
| $A_1$ | 20±1.5 |
| $A_2$ | **16±0.42** |
| $A_3$ | 29±1.75 |
| $A_4$ | 23±2.03 |

**% drug release study of batches-B1 to B9**

% drug release study was performed by using dissolution apparatus at 50 rpm & 37±5 ℃ in phosphate buffer pH 6.8. % *In-vitro* drug release of B1 to B9 batches were found to be ranging from 69.37 to 90.00%.

**Table 4: Table 5.12: In vitro dissolution study of batches-B1 to B9.**

| Time(min) | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 15.37 | 18.26 | 17.83 | 16.94 | 19.05 | 18.08 | 16.22 | 17.34 | 19.38 |
| 4 | 30.12 | 34.15 | 32.75 | 33.47 | 29.45 | 31.25 | 34.22 | 32.98 | 33.41 |
| 6 | 52.38 | 53.47 | 52.73 | 51.82 | 54.08 | 49.36 | 52.23 | 53.44 | 54.48 |
| 8 | 61.37 | 62.49 | 65.51 | 63.26 | 67.2 | 71.04 | 69.33 | 72.36 | 75.66 |
| 10 | 69.37 | 73.56 | 77.29 | 75.52 | 78.24 | 84.18 | 80.33 | 85.15 | 90 |

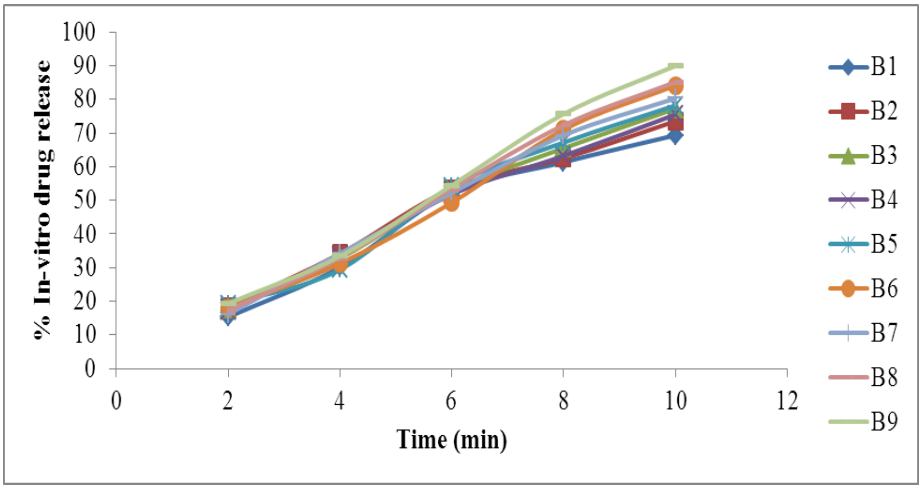


**Figure 1: % *In-vitro* drug release of Batches-B1 to B9.**

**Table 5: ANOVA for Response 1 (% In vitro drug release)**

| Analysis of variance table [Partial sum of squares - Type III] | | | | | | |
|---|---|---|---|---|---|---|
| **Source** | **Sum of Squares** | **df** | **Mean Square** | **F Value** | **p-value Prob>F** | |
| Model | 326.03 | 5 | 65.21 | 63.28 | < 0.0001 | Significant |
| A-Camphor | 114.84 | 1 | 114.84 | 111.46 | < 0.0001 | |
| B-Sodium deoxycholate | 207.21 | 1 | 207.21 | 201.10 | < 0.0001 | |
| AB | 0.77 | 1 | 0.77 | 0.74 | 0.4218 | |
| $A^2$ | 1.96 | 1 | 1.96 | 1.90 | 0.2175 | |
| $B^2$ | 0.35 | 1 | 0.35 | 0.34 | 0.5823 | |
| Residual | 6.18 | 6 | 1.03 | - | - | |
| Lack of Fit | 2.50 | 3 | 0.83 | 0.68 | 0.6204 | Notsignificant |
| Pure Error | 3.68 | 3 | 1.23 | - | - | |
| Cor Total | 332.21 | 11 | - | - | - | |

**Statistical study for response 1 (% drug release)**

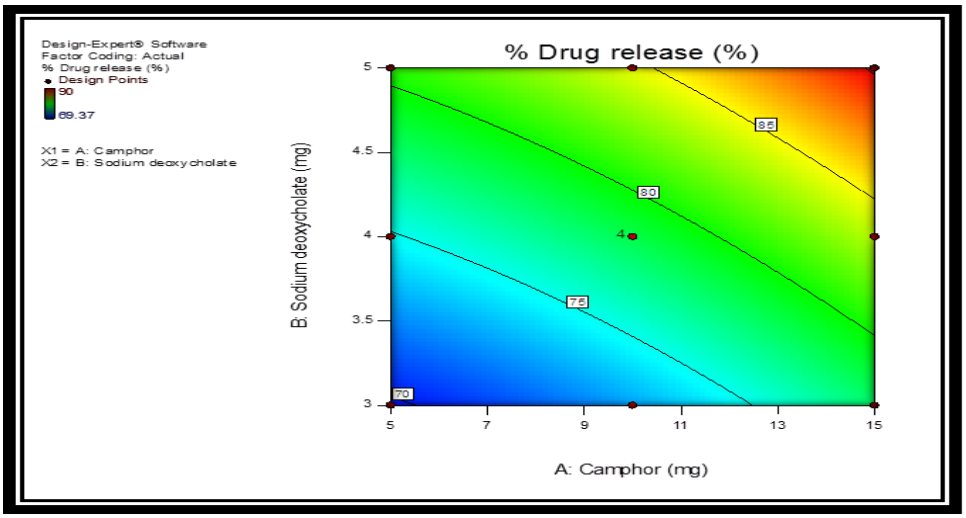


**Figure 2: Contour plot for % response-1 (*in-vitro* drug release)**

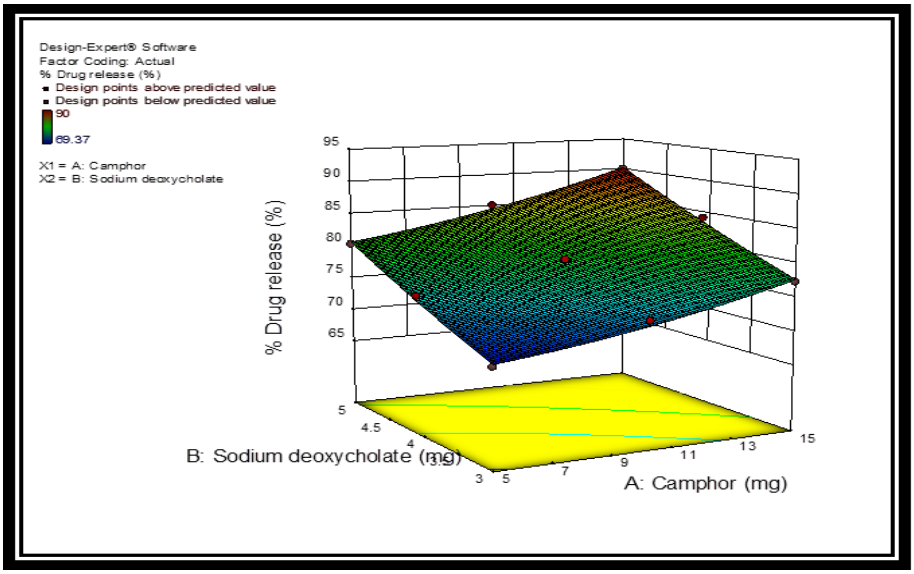


**Figure 3: Response surface plot for response-1 (% *in-vitro* drug release).**

Statistical analysis of data of % drug release was shown that both the factors, conc. of Camphor & conc. of Sodium deoxycholate, have P value <0.0001 and <0.0001 respectively were p<0.05. That indicated that both factor have significant effect on drug release. An increase in the concentration of factors leads to increase in % drug release observed.

**% Ex-vivo diffusion study of batches-B1 to B9**

Ex-vivo diffusion study was performed using Franz diffusion cell at 37.0±0.5 $^{0}$C temperature in phosphate buffer pH 6.8.

**Table 6: % Ex-vivo diffusion study of batches-B1 to B9.**

| Time(min) | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 17.35 | 15.93 | 16.05 | 18.4 | 15.1 | 17.32 | 16.03 | 18.52 | 19.04 |
| 4 | 23.04 | 25.83 | 24.07 | 22.36 | 26.1 | 25.27 | 24.62 | 26.12 | 26.2 |
| 6 | 44.27 | 46.35 | 47.44 | 45.85 | 46.07 | 47.2 | 48.63 | 49.16 | 49.31 |
| 8 | 49.3 | 52.07 | 61.69 | 51.04 | 58.21 | 61.45 | 55.13 | 60.35 | 63.22 |
| 10 | 52.26 | 58.32 | 72.33 | 56.39 | 63.51 | 75.08 | 59.18 | 71.98 | 78.46 |

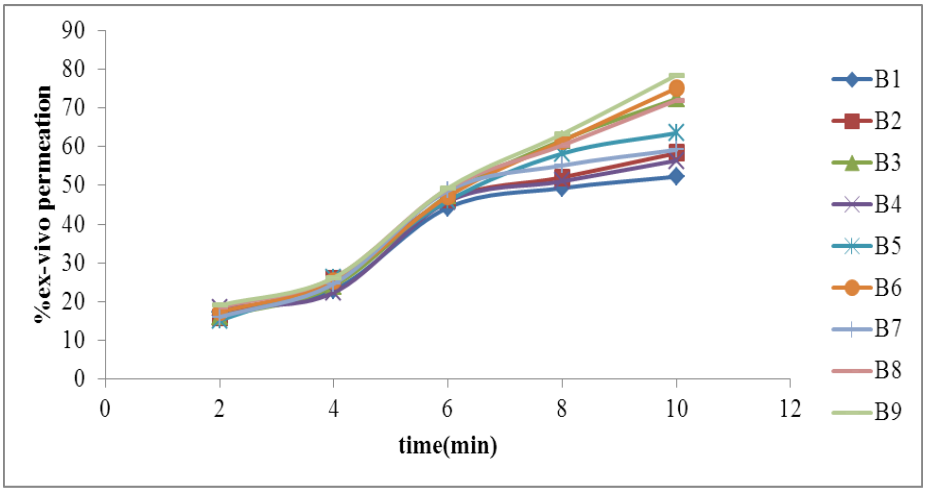


**Figure 4: % Ex-vivo drug permeation study of Batches-B1 to B9.**

**Table 7: ANOVA for Response 2 (%Ex-vivo permeation).**

| Analysis of variance table [Partial sum of squares - Type III] | | | | | | |
|---|---|---|---|---|---|---|
| **Source** | **Sum of Squares** | **df** | **Mean Square** | **F Value** | **p-value Prob>F** | |
| Model | 681.78 | 5 | 136.36 | 36.01 | 0.0002 | Significant |
| A-Camphor | 561.44 | 1 | 561.44 | 148.29 | < 0.0001 | |
| B-Sodium deoxycholate | 118.90 | 1 | 118.90 | 31.40 | 0.0014 | |
| AB | 0.16 | 1 | 0.16 | 0.041 | 0.8458 | |
| $A^2$ | 1.08 | 1 | 1.08 | 0.28 | 0.6132 | |
| $B^2$ | 6.667E-003 | 1 | 6.667E-003 | 1.761E-003 | 0.9679 | |
| Residual | 22.72 | 6 | 3.79 | - | - | |
| Lack of Fit | 17.43 | 3 | 5.81 | 3.30 | 0.1767 | not significant |
| Pure Error | 5.29 | 3 | 1.76 | - | - | |
| Cor Total | 704.50 | 11 | - | - | - | |

**Statistical study for response 2 (%Ex-vivo diffusion)**

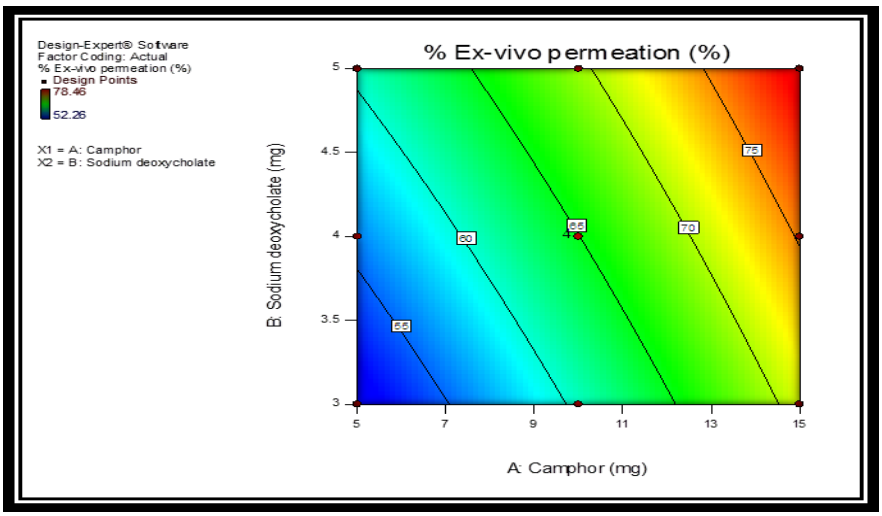


**Figure 5: Contour plot for response-2 (% *Ex-vivo permeation)***

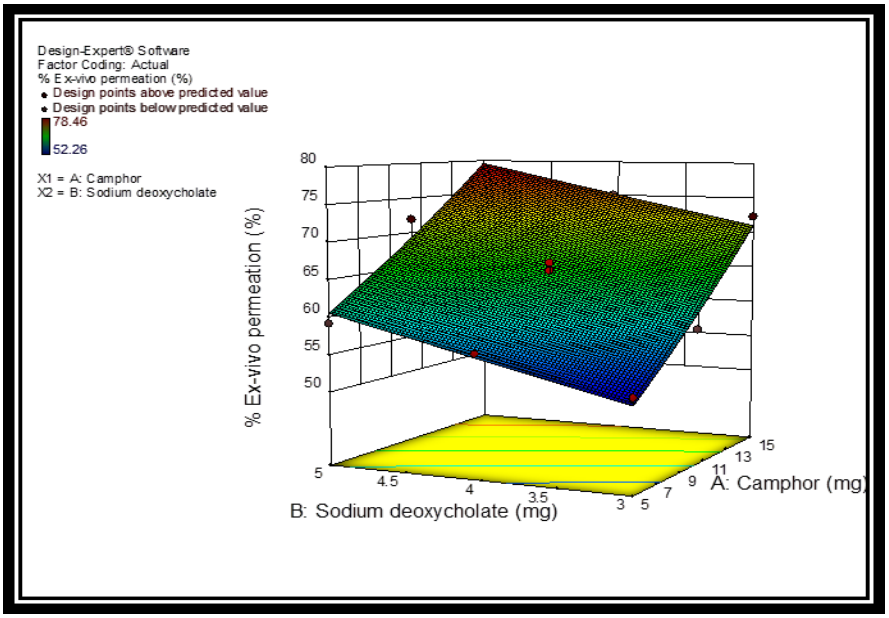


**Figure 6: Response surface plot for response-2 (% *Ex-vivo permeation)***

Statistical analysis of data of % Ex-vivo diffusion was shown that both the factors, conc. of Camphor & conc. of Sodium deoxycholate, have P value <0.0001 and 0.0014 respectively were p<0.05. That indicated that both factor have significant effect on drug release. An increase in the concentration of factors leads to increase in % permeation observed.

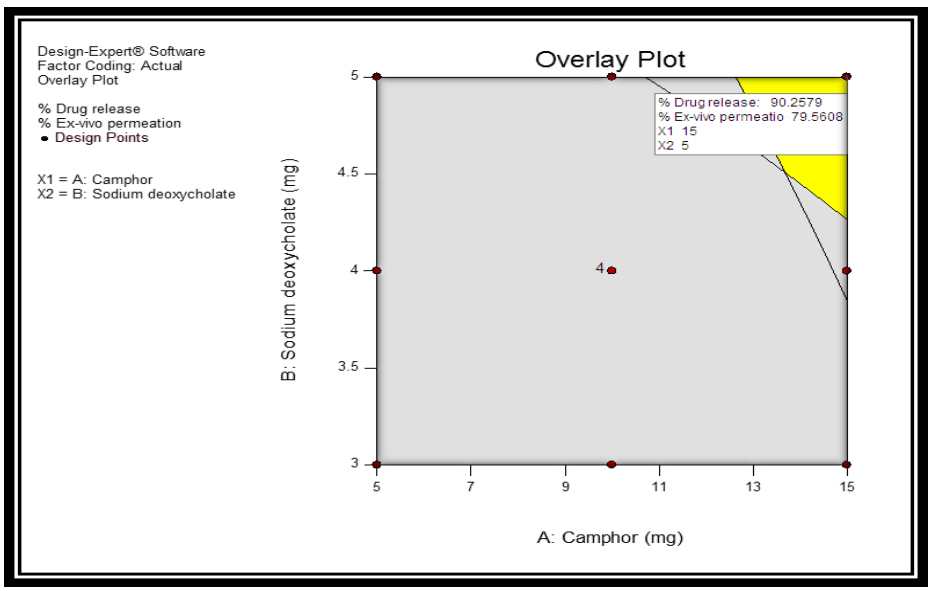


**Figure 7: Overlay plot for check-point batch study.**

The overlay plot reflects that the yellow region is the area of interest (experimental region). From the polynomial equation and the contour plots the optimized batch found was batch B9.

**% Drug release study of optimized batch-B9.**

**Table 8: % Drug release study for optimized batch-B9.**

| Time(min) | % Drug release |
|---|---|
| 2 | 19.38 |
| 4 | 33.41 |
| 6 | 54.48 |
| 8 | 75.66 |
| 10 | 90 |

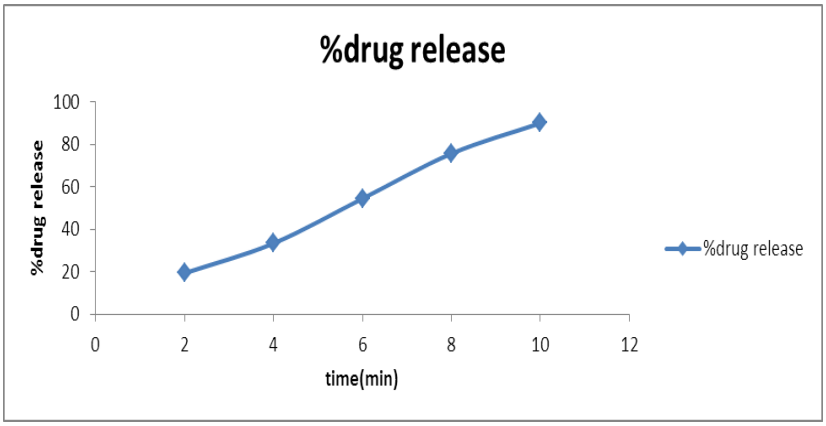


**Figure 8: % *in-vitro* drug release of optimized batch B9**

B9 Batch was given maximum drug release. So, it was selected as optimized batch.

**% Ex-vivo diffusion study of optimized batch-B9**

**Table 9: % Ex-vivo diffusion study for optimized batch-B9.**

| Time(min) | % Ex-vivo permeation |
|---|---|
| 2 | 19.04 |
| 4 | 26.2 |
| 6 | 49.31 |
| 8 | 63.22 |
| 10 | 78.46 |

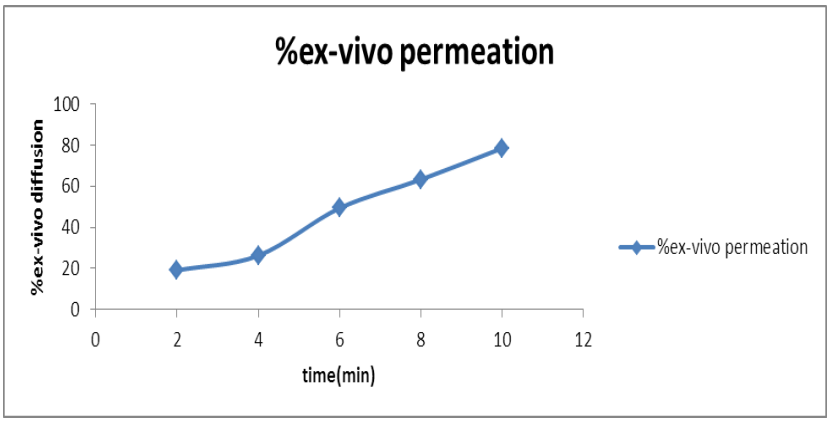


**Figure 9: %Ex-vivo diffusion of optimized batch B9**

B9 Batch was given maximum permeation. So, it was selected as optimized batch.

**Stability study**

**Table 10: Stability study of optimized batch F12.**

| Time (month) | Temperature and humidity condition | In-vitro drug release (%) | Ex-vivo diffusion study (%) |
|---|---|---|---|
| 0 | At room temperature | 90.00 | 78.46 |
| | Accelerated conditions (40$^{o}$C & 75%RH) | 90.00 | 78.46 |
| After 1 month | At room temperature | 89.42 | 78.30 |
| | Accelerated conditions (40$^{o}$C & 75%RH) | 89.15 | 77.93 |

## DISCUSSION

The stability study data for the optimized mouth dissolving tablet formulation batch containing Bambuterol Hydrochloride remain stable in terms of % In-vitro drug release and % Ex-vivo permeation at room temperature and Accelerated condition for 1 month. There is not much change in all two parameters after 1 month. So, it indicates that the optimized formulation batch is stable.

## 4. CONCLUSION

Bambuterol Hydrochloride is Antiasthmatic drug. UV spectrum of Bambuterol Hydrochloride was found 264 nm. FTIR spectra showed that drug was not having any kind of interaction with excipients. Preliminary screening was done by using different sublimable polymers like Camphor & ammonium bicarbonate and with permeation enhancers like Sodium deoxycholate & Sodium lauryl sulfate and studied their influence on results of disintegration time. Based on the result of preliminary batches Camphor and sodium deoxycholate were selected For optimization of formulation, the value of independent variables and dependent variables were statistically analyzed based on $3^2$ full factorial design by using Design Expert® 10.0.0 trial version. Total nine batches were prepared for $3^2$ factorial design. The concentration of Camphor and Sodium deoxycholate were selected as independent variables and studied their effects on responses such as % in-vitro drug release and % Ex-vivo diffusion. On basis of statistical analysis, batch B9 was found to be optimized containing 15mg Camphor and 5 mg Sodium deoxycholate. Based on linearity, drug release data fit with korsemeyer Peppas model ($R^2$ =0.992). So, Drug release mechanism was found to be Case II-Transport (n=0.982). From the experimental design, check point batch was compared with optimized formulation which shows that the model is significant. Check point batch was prepared for validation of optimized batch. It showed nearby results with predicted values. Optimized batch was tested for pre-compression and post-compression Parameters

like blend evaluation and tablet evaluation. In tablet evaluation, % *in-vitro* drug release at 10 min. and % *ex-vivo* permeation at 10 min. were found to be 90.00% and 78.46% respectively. Stability study of optimized batch B9 was performed for one month. Result of stability study showed that optimized batch B9 was found to be stable. From the result & discussion, we were observed that dissolution and permeation were induced with help of sublimable polymer and permeation enhancer by % drug release study and % Ex-vivo permeation study. The optimized formulation can be a competent alternative to conventional tablets because it may improve bioavailability of drug up to some extent as supported by ex-vivo diffusion of drug.

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